IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application Number	: 10/580,248	Confirmation No.:	6084
Applicant	: Mimi ADACHI, *et al.*		
35 U.S.C. § 371 Date	: July 20, 2006		
Title	: METHOD FOR PROLIFERATING CARDIOMYOCYTES		
TC/Art Unit	: 1632		
Examiner:	: Magdalene K. Sgagias		
Docket No.	: 64517.000003		
Customer No.	: 21967		

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APPEAL BRIEF

In response to the Office Action dated December 22, 2008 ("Office Action"), finally rejecting pending claims 1, 4-12, 15-25, 31, 34, and 35, Appellants respectfully request that the Board of Patent Appeals and Interferences reconsider and withdraw the rejections of record and allow the pending claims.

I. REAL PARTY IN INTEREST

The real party in interest is Daiichi Asubio Pharma Co., Ltd., the Assignee of the above-referenced application.[1]

II. RELATED APPEALS AND INTERFERENCES

To the best of Appellant's knowledge, there are no related Appeals or Interferences.

III. STATUS OF CLAIMS

Claims 1, 3-31, 34 and 35 are pending. Claims 3, 13, 14, and 26-30 stand withdrawn. 1, 4-12, 15-25, 31, 34, and 35 stand rejected. The rejections of claims 1, 4-12, 15-25, 31, 34, and 35 are appealed.

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[1] *See* Reel 019226, Frame 0625.

IV. STATUS OF AMENDMENTS

An amendment canceling claim 2 was filed and entered subsequent to the Office Action.[2] No other claim amendments have been filed subsequent to the Office Action.

V. SUMMARY OF CLAIMED SUBJECT MATTER

A concise explanation of independent claims 1, 17, and 34 is reproduced below, along with a citation (e.g., by page and line number) to the application as originally filed.

A. Independent claims 1 and 34 provide methods for proliferating cardiomyocytes.

Adult cardiomyocytes are generally unable to proliferate.[3] Consequently, when the heart suffers damage and a loss of cardiomyocytes, it cannot replace the lost cardiomyocytes.[4] The surviving cardiomyocytes attempt to compensate for the lost cardiomyocytes but, eventually, become exhausted and die, leading to heart failure.[5]

The claimed invention provides a method for inducing cardiomyocytes to proliferate.[6] These cardiomyocytes can replace dead or weakened cardiomyocytes, and thus can be used to treat heart disease including heart failure.[7] In particular, claims 1 and 34 are directed to a method for proliferating cardiomyocytes comprising introducing (a) cyclin, (b) cyclin-dependent kinase, and (c) one or a plurality of a gene encoding a factor that inhibits the production, function or action of Cip/Kip family protein, into cardiomyocytes *in vitro*, and culturing or maintaining said cells.[8] Claim

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[2] *See* Amendment and Response, filed March 23, 2009; *see also* Advisory Action, mailed April 10, 2009.

[3] *See* Specification, ¶ 2.

[4] *See* Specification, ¶ 2.

[5] *See* Specification, ¶ 2.

[6] *See, e.g.*, Specification, ¶ 17.

[7] *See, e.g.*, Specification, ¶¶ 29 and 31.

[8] *See, e.g.*, Specification, page 19, lines 10-17; Example 4; Figure 8; original claim 2.

34 further recites that the cardiomyocytes have withdrawn from the cell cycle.[9]

B. Independent claim 17 provides a recombinant vector comprising at least three distinct genes.

Claim 17 is directed to a vector comprising (a) a cyclin gene (b) a cyclin-dependent kinase gene, and (c) one or a plurality of a gene encoding a factor that inhibits the production, function, or action of Cip/Kip family protein.[10] This vector may be used in performing the claimed methods.[11]

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issues on appeal are:

1) Whether the rejection under 35 U.S.C. § 103(a) of claims 1, 4-12, 15-25, and 31 based on Tamamori-Adachi, *et al.* (2003) Circ. Res. 92:e12-e19 ("Adachi") in view of Sutterlüty, *et al.* (1999) Nature Cell Biology 1: 207-214 ("Sutterlüty"); Sherr and Roberts (1999) Genes & Development 13:1501-1512 ("Sherr"); Flink, *et al.* (1998) J. Mol. Cell. Cardiol. 30: 563-578 ("Flink"); and Poolman, *et al.* (1999) Circ. Res. 85: 117-127 ("Poolman") is proper.

2) Whether the rejection under 35 U.S.C. § 103(a) of claims 34 and 35 based on Adachi, Sutterlüty, Sherr, Flink, Poolman, and Carrano, *et al.* (1999) Nature Cell Biology 1: 193-199 ("Carrano") is proper.

VII. ARGUMENTS

Introduction

The USPTO alleges that Adachi teaches claim 1, elements (a) and (b), but does not teach "the introduction of a gene encoding a factor that inhibits the production or function of Cip/Kip

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[9] *See, e.g.*, Specification, ¶¶ 21 and 37.

[10] *See, e.g.*, Specification, page 17, lines 22-24; page 21, lines 14-19; original claim 17.

[11] *See, e.g.*, Specification, ¶ 17.

family proteins into cardiomyocyte cultures."[12] The USPTO contends, however, that it would have been obvious to introduce such a gene into Adachi's system in view of Sutterlüty, Sherr, Flink, and Poolman.[13]

Appellants respectfully submit that the USPTO has not established a *prima facie* case of obviousness for at least two reasons. First, the cited references alone, or in combination, do not teach or suggest each and every claim element. Indeed, Sutterlüty, Sherr, Flink, and Poolman alone, or in combination, do not teach or suggest claim 1, element (c), *i.e.*, introducing a gene encoding a factor that inhibits the production, function, or action of Cip/Kip family protein into cardiomyocytes *in vitro*. Second, even if these references did teach element (c), which they do not, there is no reason to combine this hypothetical teaching with Adachi. Indeed, the evidence of record demonstrates that the introduction of a gene encoding a factor that inhibits the production, function, or action of Cip/Kip protein ***does not*** result in the proliferation of cardiomyocytes. As such, one of ordinary skill in the art would have had no reason to combine the hypothetical teaching of element (c) with Adachi to arrive at the claimed invention.

Even assuming the USPTO properly established a *prima facie* case of obviousness, which it has not, Appellants respectfully submit that the evidence of record demonstrates unexpected results. Indeed, as discussed above, the introduction of a gene encoding a factor that inhibits the production, function, or action of Cip/Kip protein, without elements (a) and (b), does not result in the proliferation of cardiomyocytes. Thus, one of ordinary skill in the art would have expected no increase in proliferation if this gene (*e.g.*, Skp2) was introduced into cardiomyocytes and co-expressed with other genes as compared to the co-expression of these other genes alone. The specification teaches, however, that the co-expression of Skp2, cyclin D, and CDK4 resulted in a

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[12] *See* Non-Final Office Action mailed January 28, 2008, page 4.

[13] *See* Non-Final Office Action mailed January 28, 2008, page 6.

significant increase in cell number as compared to the co-expression of only cyclin D and CDK4. Accordingly, Appellants respectfully submit that the evidence of unexpected results is sufficient to overcome a *prima facie* case of obviousness.

A. The USPTO Has Not Established A *Prima Facie* Case Of Obviousness.

1. The USPTO has the burden of establishing a *prima facie* case of obviousness.

The USPTO bears the burden of establishing a *prima facie* case of obviousness.[14] There are four separate factual inquiries to consider in making an obviousness determination: (1) the scope and content of the prior art; (2) the level of ordinary skill in the field of the invention; (3) the differences between the claimed invention and the prior art; and (4) the existence of any objective evidence, or "secondary considerations," of non-obviousness.[15]

"In determining the differences between the prior art and the claims, the question under 35 U.S.C. § 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious."[16] Indeed, all claim elements must be considered when the USPTO makes an obviousness rejection.[17]

An "expansive and flexible approach" should be applied when determining obviousness based on a combination of prior art references.[18] However, a claimed invention combining multiple known elements is not rendered obvious simply because each element was known independently in

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[14] *See* M.P.E.P § 2142.

[15] *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966); *see also KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1729-1730, 82 U.S.P.Q.2d 1385, 1391 (2007) (*citing Graham v. John Deere*).

[16] *See* M.P.E.P. § 2141.02 (citing *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Schenck v. Nortron Corp.*, 713 F.2d 782, 218 USPQ 698 (Fed. Cir. 1983)).

[17] *See* M.P.E.P. § 2143.03 ("All words in a claim must be considered in judging the patentability of that claim against the prior art.") (citing *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970)).

[18] *See KSR*, 127 S. Ct. at 1739.

the prior art.[19] Rather, there must still be some "reason that would have prompted" a person of ordinary skill in the art to combine the elements in the specific way that he or she did.[20] Also, modification of a prior art reference may be obvious only if there exists a reason that would have prompted a person of ordinary skill to make the change.[21] Accordingly, an obviousness rejection "cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness."[22]

If a *prima facie* case is established, then the burden shifts to applicant to come forward with rebuttal evidence or argument to overcome the *prima facie* case.[23]

As discussed below, Appellants respectfully submit that the USPTO has failed to establish a *prima facie* case of obviousness because (1) the references alone, or in combination, do not teach each and every claim element; and (2) there is no reason to combine the references.

2. The combination of Adachi, Sutterlüty, Sherr, Flink, and Poolman does not teach claim 1, element (c).

Claim 1, element (c) requires introducing a gene encoding a factor that inhibits the production or function of a Cip/Kip protein into a cardiomyocyte *in vitro*. As discussed below, Adachi, Sutterlüty, Sherr, Flink, and Poolman alone, or in combination, do not teach or suggest claim 1, element (c).

a. The USPTO acknowledges Adachi does not teach or suggest element (c).

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[19] *See KSR*, 127 S. Ct. at 1741.

[20] *See KSR*, 127 S. Ct. at 1741; *see also In re Icon Health & Fitness, Inc.*, 496 F.3d 1374, 1380 (Fed. Cir. 2007).

[21] *See KSR*, 127 S. Ct. at 1740-41.

[22] *See* M.P.E.P. § 2141 (citing *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006); *see also KSR*, 127 S. Ct. at 1741 (quoting Federal Circuit statement with approval).

[23] *See* M.P.E.P § 2145.

The USPTO asserts that Adachi teaches a method for proliferating cardiomyocytes *in vitro* comprising introducing a cyclin (linked to nuclear localization signal) and a cyclin-dependent kinase (CDK) using two separate adenovirus vectors.[24] The USPTO concedes, however, that Adachi "differs from the claimed invention by not teaching the introduction of a gene encoding a factor that inhibits the production or function of Cip/Kip family proteins into cardiomyocyte cultures."[25]

Appellants agree that Adachi does not teach the introduction of a gene encoding a factor that inhibits the production, function, or action of Cip/Kip family protein into cardiomyocytes. Indeed, Adachi does not teach or suggest the involvement of the Cip/Kip family protein (*e.g.*, $p27^{Kip1}$) in the proliferation process of cardiomyocytes. Rather, as discussed in the specification, Adachi discloses a novel method of proliferating cardiomyocytes comprising the expression of a cyclin and a CDK.[26] Accordingly, Adachi does not teach or suggest claim element 1(c).

b. Sutterlüty does not teach or relate to methods of proliferating cardiomyocytes.

Sutterlüty relates to cell-cycle mechanisms in fibroblasts—actively dividing cells physiologically distinct from cardiomyocytes. Sutterlüty does not discuss or provide any teaching whatsoever with respect to cardiomyocytes or methods of proliferating cardiomyocytes. Rather, Sutterlüty directs one of ordinary skill in the art to consider its teachings with the development of colorectal and breast cancers.[27] Accordingly, Sutterlüty is unrelated to the claimed invention.

c. Sherr does not relate to cardiomyocytes and does not teach or suggest introducing a gene encoding a factor to inhibit production or function of a Cip/Kip protein.

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[24] *See* Office Action mailed January 28, 2008, pages 3-4.

[25] *See* Office Action mailed January 28, 2008, page 4.

[26] *See* Specification, page 3, line 13 to page 4, line 18.

[27] *See* Sutterlüty, page 213, right column, last paragraph.

Sherr, like Sutterlüty, is silent with respect to cardiomyocytes and methods of proliferating cardiomyocytes. Indeed, Sherr also suggests considering its teachings with the development of cancer.[28] Moreover, Sherr does not teach or suggest introducing a gene encoding a factor to inhibit production or function of a Cip/Kip protein. Accordingly, Sherr, like Sutterlüty, is unrelated to the claimed invention.

d. Flink does not teach or suggest the inhibition of Cip/Kip proteins, let alone teach or suggest modes of inhibiting such proteins.

According to the USPTO, "Flink by teaching that in differentiated cardiomyocytes p27 is increased, this is sufficient motivation for one of skill in the art of cell cycle regulation to degrade p27 in the cardiomyocytes of [Adachi]."[29]

Flink provides no such motivation. Flink is a general reference reporting the changes in E2F complexes containing retinoblastoma protein family members and cyclin-dependent kinase inhibitor activities during terminal differentiation of cardiomyocytes.[30] At best, Flink suggests that a paradox exists for p27, where mRNA levels are stable, but protein levels increase.[31] Flink does not discuss or provide any teachings whatsoever regarding the inhibition of Cip/Kip proteins, let alone teach or suggest modes of inhibiting such proteins. Flink is also silent on methods of proliferating cardiomyocytes.

Adachi discloses a method of proliferating cardiomyocytes by introducing a cyclin and cyclin-dependent kinase, but is silent with respect to p27.

The USPTO has not established a nexus between Flink and Adachi. Indeed, the USPTO does not provide any reasoning why one of ordinary skill in the art reading Flink would have looked

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[28] *See* Sherr, page 1501, paragraph bridging first and second columns; *see also* page 1507, right column ("A role for Cip/Kip proteins in cancer.").

[29] *See* Office Action, page 5.

[30] *See* Flink, Title.

[31] *See* Flink, abstract.

to Adachi. Accordingly, the USPTO fails to support its assertion that Flink "provides sufficient motivation ... to degrade p27 in the cardiomyocytes of [Adachi]."

e. Poolman does not teach or suggest that introducing a gene encoding a factor that inhibits the production, function or action of Cip/Kip protein.

Poolman is limited to the developmental effects of the absence (*i.e.*, the total loss) of p27 in neonatal cardiomyocytes. In particular, Poolman suggests that a genetically engineered mouse *lacking* $p27^{kip1}$ (i.e., $p27^{kip1}$ knockout mouse) showed "prolonged proliferation of cardiac myocytes."[32] Poolman does not teach or suggest inhibiting the production or function of a Cip/Kip protein, nor introducing a gene encoding a factor to accomplish such inhibition. Indeed, one of ordinary skill in the art would appreciate that the developmental events influenced by the complete absence of $p27^{kip1}$ during development are not identical to inhibiting a Cip/Kip protein. Furthermore, the specification provides evidence that almost no increase in the cell number of cardiomyocytes was observed where the production of $p27^{Kip1}$ gene product was inhibited by infection with p27 siRNA alone.[33] The USPTO acknowledges that Poolman teaches the total loss of p27, but fails to address the distinction between a knockout mouse and the introduction of a gene encoding a factor to inhibit production or function of a Cip or Kip protein.[34]

In view of the foregoing, the combination of Sutterlüty, Sherr, Flink, and Poolman does not teach or suggest a method of introducing a gene encoding a factor that inhibits production or function of Cip/Kip protein into cardiomyocytes *in vitro*. Sutterlüty and Sherr do not relate at all to cardiomyocytes or methods of proliferating cardiomyocytes. Rather, these references direct one of ordinary skill in the art to consider cell cycle mechanisms in various cancers. Flink relates to

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[32] *See* Poolman, page 126.

[33] *See* Specification, Example 5, page 82, lines 8-11, and Figures 9 and 10.

[34] *See* Amendment and Reply filed November 13, 2007, page 9.

cardiomyocytes, but is silent with respect to proliferating cardiomyocytes or inhibiting Cip/Kip proteins. Poolman discloses a p27 knockout mouse, but does not teach or suggest introducing an exogenous factor into cardiomyocytes. Accordingly, the combination of references does not teach or suggest claim 1, element (c).

3. There is no reason present in the cited references or in the knowledge generally available to one of ordinary skill in the art to combine the teachings of Sutterlüty, Sherr, Flink, and Poolman with Adachi.

Even if the combination of Sutterlüty, Sherr, Flink, and Poolman taught claim 1, element (c), which they do not, there is no reason to combine this hypothetical teaching with Adachi. Indeed, as discussed below, the specification provides evidence that the introduction of a gene (Skp2) encoding a factor that inhibits the production, function or action of Cip/Kip family protein ***does not*** result in an increase in the proliferation of cardiomyocytes. Accordingly, one of ordinary skill in the art would not have combined this gene with Adachi's system to arrive at the claimed invention.

a. The expression Skp2 alone does not result in an increase in the number of cardiomyocytes.

The specification teaches the introduction of (1) a cyclin D and a CDK4 gene; (2) a cyclin gene, a CDK4 gene, and a Skp2 gene; and (3) a Skp2 gene alone into cardiomyocytes.[35] The cell number of cardiomyocytes with the cyclin D and CDK4 genes increased about 3 fold on day 7 post-culturing.[36] The cell number of cardiomyocytes with all three genes—cyclin D, CDK4 and Skp2 increased 5 fold or more.[37] However, almost no increase of the cell numbers of cardiomyocytes infected Skp2 gene alone was observed.[38] These results demonstrate that Skp2 alone has no significant effect on the proliferation of cardiomyocytes, but when used in conjunction with a cyclin

[35] *See* Specification, Example 4.

[36] *See* Specification, Example 4.

[37] *See* Specification, Example 4.

[38] *See* Specification, Example 4.

gene and a cyclin-dependent kinase gene, the combination of the three genes more than significantly promotes the proliferation of cardiomyocytes.[39]

b. The expression $p27^{Kip1}$ siRNA alone does not result in an increase in the number of cardiomyocytes.

The specification also teaches an experiment in which cardiomyocytes transfected cyclin D, CDK4, and a siRNA specific to the $p27^{Kip1}$ gene ("p27 siRNA") were compared to cardiomyocytes transfected with cyclin D and CDK4, and cardiomyocytes transfected with p27 siRNA alone.[40] The cell number of cardiomyocytes with cyclin D and CDK4 genes increased about 3 fold on day 7 post-culturing.[41] The cell number of cardiomyocytes with all three genes (*e.g.,* cyclin D, CDK4 and p27 siRNA) were significantly increased.[42] Again, almost no increase of the cell numbers of cardiomyocytes infected with p27 siRNA alone was observed.[43] These results demonstrate that a p27 inhibitor alone (*e.g.,* p27 siRNA) has no significant effect on the proliferation of cardiomyocytes, but when used in conjunction with a cyclin gene and a cyclin-dependent kinase gene, the combination of the three genes more than significantly promotes the proliferation of cardiomyocytes.[44]

In view of the foregoing, one of ordinary skill in the art would have understood that introducing Skp2 or p27 siRNA (which inhibit the production, function, or action of a Cip/Kip family protein) into cardiomyocytes, does not result in proliferation of the cardiomyocytes. As such,

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[39] *See* Specification, Example 4.

[40] *See* Specification, Example 5.

[41] *See* Specification, Example 5.

[42] *See* Specification, Example 5.

[43] *See* Specification, Example 5.

[44] *See* Specification, Example 5.

one of ordinary skill in the art would have had no reason to introduce a gene encoding a factor that inhibits the production, function, or action of Cip/Kip family protein into Adachi's system.

4. The combination of references does not teach or suggest claims 34 and 35.

Claims 34 and 35 are drawn to methods of proliferating cardiomyocytes that have withdrawn from the cell cycle (*e.g.*, adult cardiomyocytes) comprising introducing (a) cyclin, (b) cyclin-dependent kinase, and (c) one or a plurality of a gene encoding a factor that inhibits the production, function or action of Cip/Kip family protein, into cardiomyocytes.

As discussed above, Adachi, Sutterlüty, Sherr, Flink, and Poolman alone, or in combination, fails to teach or suggest element (c). Carrano does not remedy this deficiency. Indeed, Carrano, like Sutterlüty and Sherr, does not relate to cardiomyocytes or methods of proliferating cardiomyocytes. Rather, Carrano directs one of ordinary skill in the art to consider cell cycle mechanisms in cancer.[45] Accordingly, because Adachi, Sutterlüty, Sherr, Flink, Poolman, and Carrano alone, or in combination, fail to teach or suggest element (c), the rejection over claims 34 and 35 should be withdrawn.

5. The combination of Adachi, Sutterlüty, Sherr, Flink, and Poolman do not teach or suggest the claimed vectors.

Claim 17 is directed a vector comprising a cyclin gene, a CDK gene and a gene encoding a factor that inhibits the production, function or action of Cip/Kip family protein.

Adachi teaches two separate adenovirus vectors: one vector comprising a cyclin D1 gene and a different vector comprising a CDK4 gene.[46] Adachi does not teach or suggest a single vector comprising a cyclin gene, a CDK gene and a gene encoding a factor that inhibits the production, function or action of Cip/Kip family protein.

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[45] *See* Carrano, page 193, first column, first paragraph and page 198, second column, last paragraph.

[46] *See* Adachi, "Adenoviruses", page 2.

Sutterlüty, Sherr, Flink, and Poolman do not remedy this deficiency. Indeed, these references alone, or in combination, do not teach or suggest modifying Adachi's two vector system to include an additional gene and then combine three genes into a single vector. Furthermore, the USPTO has not provided any reason why one of ordinary skill in the art would have combined Adachi, Sutterlüty, Sherr, Flink, and Poolman to arrive at the claimed vectors. Appellants have raised this issue on several occasions.[47] Accordingly, Appellants respectfully request withdrawal of this rejection.

It will be appreciated that, even post-*KSR*, it is still not sufficient merely to allege that the combination of claimed elements can be found in the prior art. For example, in *Innogenetics N.V. v. Abbott Labs.*,[48] the Federal Circuit considered an allegation of obviousness based on a combination of references and expert testimony that they were obvious to combine so as to arrive at the invention. The court acknowledged that it was "mindful that in *KSR*, the Supreme Court made clear that a finding of teaching, suggestion, or motivation to combine is not a 'rigid rule that limits the obviousness inquiry.'"[49] Here, however, "[t]here was a complete absence of any proof that one skilled in the art would find the particular claimed method obvious based upon [the expert's] list of prior art references or the knowledge generally available to those of ordinary skill in the art for any reason."[50] The court noted that "[w]e must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention."[51]

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[47] *See* Applicants' response, filed November 13, 2007, page 10, footnote 1; *see also* Applicants' response filed July 28, 2008, page 10.

[48] *Innogenetics N.V. v. Abbott Labs.*, 512 F.3d 1363, 85 U.S.P.Q 1641 (Fed. Cir. 2008).

[49] *Id.* at 1374 n.3 (citing *KSR* at 1741).

[50] *Id.* (emphasis in original).

[51] *Id.*

This is precisely what the USPTO has done in this case. Indeed, the USPTO fails to provide a clear rationale for combining the cited references. Moreover, the USPTO does not address Appellants' evidence and arguments that one of ordinary skill in the art would not have had a reason to introduce a gene encoding a factor that inhibits the production, function, or action of Cip/Kip family protein into Adachi's system. Rather, the prosecution history makes clear that the USPTO, using the invention as a starting point, compiled a disparate collection of references to attempt to arrive at the claimed invention. Such reasoning is insufficient to establish a *prima facie* case of obviousness.

In view of the foregoing, Appellants respectfully submit that because the USPTO has not established a *prima facie* case of obviousness, the rejections should be withdrawn.

B. The Evidence of Record Demonstrates Unexpected Results.

It is well established under 35 U.S.C. § 103 that even if the Patent Office makes out a *prima facie* case of obviousness, an Applicant may rebut such *prima facie* case by demonstrating unexpected results.[52]

As discussed above, the specification demonstrates that the introduction of a gene encoding a factor that inhibits the production, function, or action of Cip/Kip protein does not result in the proliferation of cardiomyocytes. Indeed, Examples 4 and 5 show that the introduction of Skp2 or p27 siRNA alone into cardiomyocytes did not result in an increase in the cell number of cardiomyocytes. As such, one of ordinary skill in the art would have expected that if Skp2, for example, was introduced into cardiomyocytes and co-expressed with other genes (e.g., cyclin D and CDK4), there would not be an increase in proliferation of the cardiomyocytes as compared to the co-expression of these other genes (e.g., cyclin D and CDK4) alone. The specification teaches,

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[52] *See* M.P.E.P § 2145.

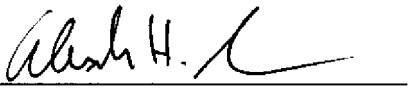
however, that the co-expression of Skp2, cyclin D, and CDK4 resulted in a significant increase in cell number as compared to the co-expression of only cyclin D and CDK4. This result is surprising and unexpected.[53] Accordingly, even assuming the USPTO established a *prima facie* case of obviousness, which it has not, Appellants respectfully submit that the evidence of unexpected results is sufficient to overcome the *prima facie* case of obviousness.

VIII. CONCLUSION

In view of the foregoing, Appellants respectfully requests that the Board of Patent Appeals and Interferences reverse the prior art rejections set forth in the Office Action, and allow all of the pending claims.

Respectfully submitted,
HUNTON & WILLIAMS LLP

Date: September 22, 2009

By: 

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[53] Appellants have also shown that the introduction of Skp2, cyclin D, and CDK4 into cardiomyocytes improves cardiac function. *See* Specification, Example 6.

IX. CLAIMS APPENDIX

1. (**Previously Presented**) A method for proliferating cardiomyocytes comprising a step of introducing
   (a) cyclin,
   (b) cyclin-dependent kinase, and
   (c) one or a plurality of a gene encoding a factor that inhibits the production, function or action of Cip/Kip family protein, into cardiomyocytes *in vitro*, and a step of subsequently culturing or maintaining said cells.

2. (**Canceled**)

3. (**Withdrawn**) A method for proliferating cardiomyocytes comprising a step of introducing
   (a) cyclin,
   (b) cyclin-dependent kinase, and
   (c) one or a plurality of a gene encoding a factor that inhibits the production, function or action of Cip/Kip family protein, or a nucleic acid that inhibits the production of Cip/Kip family protein, into cardiomyocytes *in vivo*, and
   a step of subsequently maintaining said cells.

4. (**Previously Presented**) The method of claim 1, wherein said cyclin is a cyclin that activates CDK4 or CDK6 of mammals.

5. (**Original**) The method of claim 4, wherein said cyclin is cyclin D of mammals.

6. (**Previously Presented**) The method of claim 1, wherein said cyclin-dependent kinase is a cyclin-dependent kinase to be activated by cyclin D.

7. (**Previously Presented**) The method of claim 6, wherein said cyclin dependent kinase is CDK4 or CDK6.

8. (**Previously Presented**) The method of claim 1, wherein the Cip/Kip family protein is $p27^{Kip1}$.

9. (**Previously Presented**) The method of claim 1, wherein the factor that inhibits the production, function, or action of Cip/Kip family protein is a factor with an action to promotes the degradation of the Cip/Kip family protein.

10. (**Original**) The method of claim 9, wherein the factor with an action to promote the degradation of the Cip/Kip family protein is a component of ubiquitin ligase.

11. (**Previously Presented**) The method of claim 10, wherein the component of ubiquitin ligase is an F-box factor that binds to the Cip/Kip family protein.

12. (**Original**) The method of claim 11, wherein the F-box factor capable of binding to the Cip/Kip family protein is Skp2.

13. (**Withdrawn**) The method of claim 1, wherein the nucleic acid that inhibits the production of Cip/Kip family protein is siRNA specific to a gene encoding the Cip/Kip family protein.

14. (**Withdrawn**) The method of claim 13, wherein the nucleic acid that inhibits the production of Cip/Kip family protein is siRNA specific to the $p27^{Kip1}$ gene.

15. (**Previously Presented**) The method of claim 1, comprising introducing the genes into cardiomyocytes, using a viral vector or liposome.

16. (**Previously Presented**) The method of claim 1, wherein at least one of the cyclin gene and cyclin-dependent kinase gene is tagged with a nucleotide sequence encoding a nuclear localization signal.

17. (**Previously Presented**) A vector comprising

    (a) a cyclin gene

(b) a cyclin-dependent kinase gene, and

(c) one or a plurality of a gene encoding a factor that inhibits the production, function, or action of Cip/Kip family protein.

18. (**Previously Presented**) The vector of claim 17, wherein the cyclin is a cyclin that activates CDK4 or CDK6 of mammals.

19. (**Original**) The vector of claim 18, wherein the cyclin is cyclin D of mammals.

20. (**Previously Presented**) The vector of claim 17, wherein the cyclin-dependent kinase is a cyclin-dependent kinase to be activated by cyclin D.

21. (**Original**) The vector of claim 20, wherein the cyclin-dependent kinase is CDK4 or CDK6.

22. (**Previously Presented**) The vector of claim 17, wherein the factor that inhibits the production, function, or action of Cip/Kip family protein is a factor with an action to promote the degradation of the Cip/Kip family protein.

23. (**Original**) The vector of claim 22, wherein the factor with an action to promote the degradation of the Cip/Kip family protein is a component of ubiquitin ligase.

24. (**Original**) The vector of claim 23, wherein the component of ubiquitin ligase is an F-box factor capable of binding to the Cip/Kip family protein.

25. (**Original**) The vector of claim 24, wherein the F-box factor capable of binding to the Cip/Kip family protein is Skp2.

26. (**Withdrawn**) The vector of claim 17, wherein the nucleic acid that inhibits the production of Cip/Kip family protein is siRNA specific to a gene encoding the Cip/Kip family protein.

27. (**Withdrawn**) The vector of claim 26, wherein the nucleic acid that inhibits the production of Cip/Kip family protein is siRNA that is specific to $p27^{Kip1}$ gene.

28. (**Withdrawn**) The vector of claim 17, wherein at least one of the cyclin gene and cyclin-dependent kinase gene is tagged with a nucleotide sequence encoding a nuclear localization signal.

29. (**Withdrawn**) A pharmaceutical composition for use in a treatment of cardiac disorder comprising the vector of claim 17.

30. (**Withdrawn**) The pharmaceutical composition of claim 29, wherein the cardiac disorder is myocardial infarction, ischemic heart disease, congestive heart failure, hypertrophic cardiomyopathy, dilated cardiomyopathy, myocarditis, or chronic heart failure.

31. (**Previously Presented**) Cardiomyocyte obtained by the method of claim 1.

Claims 32-33 (**Cancelled**)

34. (**Previously Presented**) A method for proliferating cardiomyocytes that have withdrawn from the cell cycle comprising a step of introducing

    (a) cyclin,

    (b) cyclin-dependent kinase, and

    (c) one or a plurality of a gene encoding a factor that inhibits the production, function or action of Cip/Kip family protein, into cardiomyocytes *in vitro*, wherein said cardiomyocytes have withdrawn from the cell cycle, and a step of subsequently culturing or maintaining said cells.

35. (**Previously Presented**) The method of claim 34, wherein the cardiomyocytes are adult cardiomyocytes.

X. EVIDENCE APPENDIX

None.

XI. RELATED PROCEEDINGS APPENDIX

None